

WHAT IS CLAIMED IS:

1. A hapten-carrier conjugate comprising:
 - (a) a carrier comprising at least one first attachment site, and
 - (b) at least one hapten with at least one second attachment site; wherein said carrier comprises, preferably being a core particle and; wherein said second attachment site is capable of association through at least one covalent bond to said first attachment site so as to form an ordered and repetitive hapten-carrier conjugate.
2. The conjugate of claim 1, wherein said core particle is selected from the group consisting of:
 - (i) a virus;
 - (ii) a virus-like particle;
 - (iii) a bacteriophage;
 - (iv) a virus-like particle of a RNA-phage;
 - (v) a bacterial pilus;
 - (vi) a viral capsid particle; and
 - (vii) a recombinant form of (i), (ii), (iii), (iv), (v) or (vi).
3. The conjugate of claim 1, wherein said core particle comprises, preferably is, a virus-like particle, wherein preferably said virus-like particle is a recombinant virus-like particle.
4. The conjugate of claim 3, wherein said virus-like particle comprises one or more recombinant proteins or fragments thereof, being selected from the group consisting of:
 - (a) recombinant proteins of Hepatitis B virus;
 - (b) recombinant proteins of measles virus;
 - (c) recombinant proteins of Sindbis virus;
 - (d) recombinant proteins of Rotavirus;

- (e) recombinant proteins of Foot-and-Mouth-Disease virus;
- (f) recombinant proteins of Retrovirus;
- (g) recombinant proteins of Norwalk virus;
- (h) recombinant proteins of Alphavirus;
- (i) recombinant proteins of human Papilloma virus;
- (j) recombinant proteins of Polyoma virus;
- (k) recombinant proteins of bacteriophages;
- (l) recombinant proteins of RNA-phages;
- (m) recombinant proteins of Ty;
- (n) recombinant proteins of Q β -phage;
- (o) recombinant proteins of GA-phage
- (p) recombinant proteins of fr-phage
- (q) recombinant proteins of AP205 phage; and
- (r) fragments of any of the recombinant proteins from (a) to (q).

- 5. The conjugate of claim 3, wherein said virus-like particle comprises a Hepatitis B virus capsid protein.
- 6. The conjugate of claim 5, wherein the amino acid sequence of the Hepatitis B capsid protein is at least about 80% identical to the sequence of SEQ ID No: 1.
- 7. The conjugate of claim 5, wherein said coat proteins have been modified by deletion of at least one lysine residue, by addition of at least one lysine residue by way of insertion, or substitution for at least one lysine residue.
- 8. The conjugate of claim 3, wherein said virus-like particle comprises, or alternatively consists of, recombinant proteins, or fragments thereof, of a RNA-phage.
- 9. The conjugate of claim 8, wherein RNA-phage is selected from the group consisting of:

- (a) bacteriophage Q β ;
- (b) bacteriophage R17;
- (c) bacteriophage fr;
- (d) bacteriophage GA;
- (e) bacteriophage SP;
- (f) bacteriophage MS2;
- (g) bacteriophage M11;
- (h) bacteriophage MX1;
- (i) bacteriophage NL95;
- (j) bacteriophage f2
- (k) bacteriophage AP205; and
- (l) bacteriophage PP7.

10. The conjugate of claim 3 wherein said virus-like particle comprises, or alternatively consists of, recombinant proteins, or fragments thereof, of RNA-phage Q β .
11. The conjugate of claim 3 wherein said virus-like particle comprises, or alternatively consists of, recombinant proteins, or fragments thereof, of RNA-phage fr.
12. The conjugate of claim 3 wherein said virus-like particle comprises, or alternatively consists of, recombinant proteins, or fragments thereof, of RNA-phage AP205.
13. The conjugate of claim 8, wherein the recombinant proteins comprise, or alternatively consist essentially of, or alternatively consist of coat proteins of RNA phages.
14. The conjugate of claim 13, wherein said coat proteins of RNA phages having an amino acid are selected from the group consisting of:
 - (a) SEQ ID NO:3;
 - (b) a mixture of SEQ ID NO:3 and SEQ ID NO:4;

- (c) SEQ ID NO:24;
- (d) SEQ ID NO:25;
- (e) SEQ ID NO:26;
- (f) SEQ ID NO:27;
- (g) a mixture of SEQ ID NO:27 and SEQ ID NO:28;
- (h) SEQ ID NO:29;
- (i) SEQ ID NO:30;
- (j) SEQ ID NO:31;
- (k) SEQ ID NO:32;
- (l) SEQ ID NO:33;
- (m) SEQ ID NO:13; and
- (n) SEQ ID NO:14.

15. The conjugate of claim 8, wherein said recombinant proteins of said RNA phage comprise or alternatively consist essentially of, or alternatively consist of one or more mutant coat proteins of RNA-phages.

16. The conjugate of claim 15, wherein said RNA-phage is selected from the group consisting of:

- (a) bacteriophage Q β ;
- (b) bacteriophage R17;
- (c) bacteriophage fr;
- (d) bacteriophage GA;
- (e) bacteriophage SP;
- (f) bacteriophage MS2;
- (g) bacteriophage M11;
- (h) bacteriophage MX1;
- (i) bacteriophage NL95;
- (k) bacteriophage f2;
- (l) bacteriophage PP7; and
- (m) bacteriophage AP205.

17. The conjugate of claim 16, wherein said mutant coat proteins of said RNA phage have been modified by removal of at least one lysine residue by way of substitution.
18. The conjugate of claim 16, wherein said mutant coat proteins of said RNA phage have been modified by addition of at least one lysine residue by way of substitution.
19. The conjugate of claim 16, wherein said mutant coat proteins of said RNA phage have been modified by deletion of at least one lysine residue.
20. The conjugate of claim 16, wherein said mutant coat proteins of said RNA phage have been modified by addition of at least one lysine residue by way of insertion.
21. The conjugate of claim 8, wherein said recombinant proteins comprise coat proteins having an amino acid sequence as set forth in SEQ ID NO:3, or a mixture of coat proteins having amino acid sequences of SEQ ID NO: 4, or mutants thereof, and of SEQ ID NO:3.
22. The conjugate of claim 8, wherein said virus-like particle essentially consisting of coat proteins having an amino acid sequence of SEQ ID NO:3, or essentially consisting of a mixture of coat proteins having amino acid sequences of SEQ ID NO: 4, or mutants thereof, and of SEQ ID NO:3.
23. The conjugate of claim 10, wherein said recombinant proteins comprise mutant Q β coat proteins.
24. The conjugate of claim 23, wherein said mutant Q β coat proteins have been modified by removal of at least one lysine residue by way of substitution, or by addition of at least one lysine residue by way of substitution.

25. The conjugate of claim 23, wherein said mutant Q β coat proteins have been modified by deletion of at least one lysine residue, or by addition of at least one lysine residue by way of insertion.
26. The conjugate of claim 23, wherein said mutant Q β coat proteins comprise proteins having an amino acid sequence selected from the group consisting of:
 - (a) the amino acid sequence of SEQ ID NO:6;
 - (b) the amino acid sequence of SEQ ID NO:7;
 - (c) the amino acid sequence of SEQ ID NO:8;
 - (d) the amino acid sequence of SEQ ID NO:9; and
 - (e) the amino acid sequence of SEQ ID NO:10.
27. The conjugate of claim 2, wherein said virus-like particle consisting essentially of mutant Q β coat proteins having an amino acid sequence selected from the group consisting of:
 - (a) the amino acid sequence of SEQ ID NO:6;
 - (b) the amino acid sequence of SEQ ID NO:7;
 - (c) the amino acid sequence of SEQ ID NO:8;
 - (d) the amino acid sequence of SEQ ID NO:9;
 - (e) the amino acid sequence of SEQ ID NO:10.
28. The conjugate of claim 1, wherein said first attachment sites comprise:
 - (a) an amino group;
 - (b) a carboxyl group;
 - (c) a sulfhydryl group;
 - (d) a hydroxy group;
 - (e) a guanidinyl group; or
 - (f) a histidinyl group.
29. The conjugate of claim 1, wherein said at least one first attachment site is selected from a lysine residue, an arginine residue, a cysteine residue, an

aspartate, a glutamate residue, a serine residue, a threonine residue, a histidine residue and a tyrosine residue.

30. The conjugate of claim 1, wherein said at least one first attachment site is a lysine residue.
31. The conjugate of claim 1, wherein said second attachment site is capable of association to said first attachment site through at least one non-peptide bond.
32. The conjugate of claim 1, wherein said hapten is an organic molecule suited to induce an immune response against a drug, hormone or toxin.
33. The hapten-carrier conjugate of claim 1 wherein said hapten is suitable for eliciting an immune response against a drug.
34. The conjugate of claim 33, wherein said drug is addictive or a drug of abuse.
35. The conjugate of claim 33 wherein said drug is selected from the group consisting of:
 - (a) codeine;
 - (b) fentanyl;
 - (c) heroin;
 - (d) morphine;
 - (e) amphetamine;
 - (f) cocaine;
 - (g) methylenedioxymethamphetamine;
 - (h) methamphetamine;
 - (i) methylphenidate;
 - (j) nicotine;
 - (k) cotinine;
 - (l) nornicotine;
 - (m) PCP;

- (n) LSD;
- (o) mescaline;
- (p) psilocybin;
- (q) tetrahydrocannabinol;
- (r) diazepam;
- (s) desipramine;
- (t) imipramine;
- (u) nortriptyline; and
- (v) the amitriptyline class of drugs.

36. The conjugate of claim 33, wherein said drug is nicotine, cotinine or nornicotine.

37. The conjugate of claim 33, wherein said drug is nicotine.

38. The conjugate of claim 36, wherein the conjugate is formed from starting materials selected from the group consisting of:

- (a) 6-(carboxymethylureido)-(\pm)-nicotine (CMUNic);
- (b) trans-3'-aminomethylnicotine succinate;
- (c) O-succinyl-3'-hydroxymethyl-nicotine;
- (d) Trans-4'-carboxycotinine;
- (e) N-[1-oxo-6-[(25)-2-(3-pyridyl)-1-pyrrolidinyl] hexyl]- β -alanine;
- (f) 4-oxo-4-[[6-[(5S)-2-oxo-5-(3-pyridinyl)-1-pyrrolidinyl]]hexyl]amino]-butanoic acid;
- (g) (2S)-2-(3-pyridinyl)-1-pyrrolidinebutanoic acid phenylmethyl ester;
- (h) (2R)-2-(3-pyridinyl)-1-pyrrolidinebutanoic acid phenylmethyl ester;
- (i) Cotinine 4'-carboxylic acid, N-succinyl-6-amino-(\pm)-nicotine;
- (j) 6-(.sigma.-aminocapramido)-(\pm)-nicotine;
- (k) 6-(.sigma.-aminocapramido)-(\pm)-nicotine;
- (l) 3' aminomethylnicotine;
- (m) 4' aminomethylnicotine;

- (n) 5' aminomethylnicotine;
- (o) 5 aminonicotine;
- (p) 6 aminonicotine;
- (q) S-1-(b-aminoethyl) nicotinium chloride; and
- (r) S-1-(b-aminoethyl) cotinium chloride.

39. The conjugate of claim 36 wherein said hapten comprises the starting material O-succinyl-3'-hydroxymethyl-nicotine.

40. The conjugate of claim 36, wherein said conjugate comprises O-succinyl-3'-hydroxymethyl-nicotine conjugated to Q β virus like particle.

41. The conjugate of claim 36 wherein said hapten is formed from the starting material O-succinyl-3'-hydroxymethyl-nicotine.

42. The conjugate of claim 41, wherein the second attachment site contains, preferably is, an active group selected from the group consisting of

- (a) Amine;
- (b) Amide;
- (c) Carboxyl;
- (d) Sulfhydryl;
- (e) Hydroxyl;
- (f) Aldehyde;
- (g) Diazonium;
- (h) Alcyhalogenid;
- (i) Hydrazine;
- (j) Vinyl;
- (k) Maleimid;
- (l) Succinimide; and
- (m) Hydrazide.

43. The conjugate of claim 42, wherein said second attachment site is formed by reaction of the O-succinyl moiety of said O-succinyl-3'-hydroxymethyl-nicotine with the first attachment site.

44. The conjugate of claim 41, wherein the second attachment site contains, preferably is, an amide.
45. The conjugate of claim 44, wherein said second attachment site is formed by reaction of the O-succinyl moiety of said O-succinyl-3'-hydroxymethyl-nicotine with a lysine residue being said first attachment site.
46. The conjugate of claim 36, wherein said conjugate comprises O-succinyl-3'-hydroxymethyl-nicotine conjugated to a virus-like particle of a RNA-phage, preferably to a Q β virus like particle, and hereby preferably to a Q β virus like particle comprising, or preferably being composed of coat proteins of .RNA-phage Q β .
47. The conjugate of claim 33, wherein the second attachment site contains an active group selected from the group consisting of
 - (a) Amine;
 - (b) Amide;
 - (c) Carboxyl;
 - (d) Sulfhydryl;
 - (e) Hydroxyl;
 - (f) Aldehyde;
 - (g) Diazonium;
 - (h) Alcyhalogenid;
 - (i) Hydrazine;
 - (j) Vinyl;
 - (k) Maleimid;
 - (l) Succinimide; and
 - (m) Hydrazide.
48. The conjugate of claim 33, wherein the addictive drug or drug of abuse is cocaine.

49. The conjugate of claim 48 wherein the conjugate is formed from starting materials selected from the group consisting of
 - (a) diazonium salt of benzoyl cocaine;
 - (b) diazonium salt of benzoyl ecognine;
 - (c) acylated ecgonine methyl ester;
 - (d) succinylated ecgonine methyl ester;
 - (e) succinylated norcocaine;
 - (f) Norcocaine; and
 - (g) benzoyl ecgonine.
50. The conjugate of claim 49, wherein the second attachment site contains an active group selected from the group consisting of
 - (a) Amine;
 - (b) Amide;
 - (c) Carboxyl;
 - (d) Sulfhydryl;
 - (e) Hydroxyl;
 - (f) Aldehyde;
 - (g) Diazonium;
 - (h) Alcyhalogenid;
 - (i) Hydrazine;
 - (j) Vinyl;
 - (k) Maleimid;
 - (l) Succinimide; and
 - (m) Hydrazide.
51. A composition suitable for treating or preventing addiction to a drug comprising the conjugate of claim 34 and a pharmaceutically acceptable excipient.
52. The composition of claim 51, further comprising an adjuvant.
53. A method of treating or preventing addiction to a drug, said method comprising administering to an individual the conjugate of claim 34.

54. A method of treating or preventing addiction to a drug, said method comprising administering to an individual an antibody directed against the conjugate of claim 34.

55. The conjugate of claim 1, wherein said hapten is a hormone.

56. The composition of claim 55 wherein the hormone is selected from the group comprising:

- (a) Progesterone;
- (b) Estrogen;
- (c) Testosterone;
- (d) follicle stimulating hormone;
- (e) melanin stimulating hormone;
- (f) adrenalin;
- (g) noradrenalin; and
- (h) fragments of any one of (a)-(e).

57. The composition of claim 56, wherein the second attachment site contains an active group selected from the group consisting of

- (a) Amine;
- (b) Amide;
- (c) Carboxyl;
- (d) Sulfhydryl;
- (e) Hydroxyl;
- (f) Aldehyde;
- (g) Diazonium;
- (h) Alcyhalogenid;
- (i) Hydrazine;
- (j) Vinyl;
- (k) Maleimid;
- (l) Succinimide; and
- (m) Hydrazide.

58. The conjugate of claim 1 wherein said hapten is a toxin.
59. The conjugate of claim 58, wherein the toxin is selected from the group comprising of:
 - (a) Aflatoxin;
 - (b) ciguatera toxin;
 - (c) tetrodotoxin;
 - (d) an antibiotic; and
 - (e) an anticancer agent.
60. The conjugate of claim 58, wherein the toxin is a metabolite generated in the body of an animal.
61. The conjugate of claim 60, wherein the metabolite is further a metabolite of a pharmaceutical agent.
62. The conjugate of claim 58, wherein said toxin is a chemical warfare agent.
63. A pharmaceutical composition comprising the conjugate of any one of claims 33, 55, or 58; and a pharmaceutically acceptable carrier.
64. The pharmaceutical composition of claim 63 further comprising an adjuvant.
65. The pharmaceutical composition of claim 63, wherein said composition is devoid of an adjuvant.
66. A vaccine composition comprising the conjugate of any of claims 1 or 33.
67. The vaccine composition of claim 66, further comprising an adjuvant.
68. The vaccine composition of claim 66, wherein said vaccine composition is devoid of an adjuvant.

69. A method of inducing an immune response to a drug in an animal, said method comprising administering an immunologically effective amount of the conjugate of claim 33 to an animal and permitting said animal to produce an immune response to said drug.
70. The method of claim 69, wherein said conjugate is administered to said animal by a route selected from the group consisting of: intranasally, orally, subcutaneously, transdermally, intramuscularly or intravenously.
71. The method of claim 70 wherein the route is intranasal.
72. The method of claim 70 involving more than one immunization.
73. The method of claim 72, wherein the immunizations are by the same, or different routes.
74. The method of claim 69, wherein said drug is selected from the group consisting of from the group consisting of:
 - (a) codeine;
 - (b) fentanyl;
 - (c) heroin;
 - (d) morphine;
 - (e) amphetamine;
 - (f) cocaine;
 - (g) methylenedioxymethamphetamine;
 - (h) methamphetamine
 - (i) methylphenidate;
 - (j) nicotine;
 - (k) cotinine;
 - (l) nornicotine;
 - (m) PCP;
 - (n) LSD;
 - (o) mescaline;
 - (p) psilocybin;

- (q) tetrahydrocannabinol;
- (r) diazepam;
- (s) desipramine;
- (t) imipramine;
- (u) nortriptyline; and
- (v) the amitriptyline class of drugs.

75. An antibody that recognizes a hapten, said antibody produced by immunization of an animal with the composition of claim 63.

76. A composition comprising an antibody or Fab fragment against a hapten, said antibody or Fab fragment generated by immunization of an animal with the hapten-carrier conjugate comprising:

- (a) a carrier with at least one first attachment site, and
- (b) at least one hapten with at least one second attachment; wherein said carrier is a core particle; and wherein said second attachment site is capable of association through at least one covalent bond to said first attachment site so as to form an ordered and repetitive hapten-carrier conjugate.

77. The antibody composition of claim 76, wherein the antibody is monoclonal.

78. The antibody or Fab fragment of claim 76, which is humanized.

79. A method for detecting a hapten with the antibody or Fab fragment of claim 76.

80. The method of claim 79, where the method is an ELISA, Radioimmunoassay, Western blot, or FACS.

81. A method of treating addiction in an individual by the administration to said individual the antibody or Fab fragment of claim 76.

82. A method of preventing addiction by the administering to an individual the antibody or Fab fragment of claim 76.
83. A method of claim 76 wherein the individual is immunocompromised.
84. A method of preventing or treating diseases associated with addiction by administering to an animal the antibody or Fab fragment of claim 76.
85. A method of preventing or treating diseases associated with addiction by administering to an animal the composition of claim 63.
86. A kit for detecting nicotine, said kit comprising an antibody or Fab fragment against nicotine, said antibody or Fab fragment generated by immunization of an animal with a hapten-carrier conjugate comprising:
 - (a) a carrier with at least one first attachment site, and
 - (b) at least one nicotine hapten with at least one second attachment; wherein said carrier is a virus-like particle; and wherein said second attachment site is capable of association through at least one covalent bond to said first attachment site so as to form an ordered and repetitive nicotine hapten-carrier conjugate.
87. A method for treating or preventing nicotine addiction in animal, said method comprising administering to an animal an immunologically effective amount of a nicotine hapten-carrier conjugate comprising:
 - (a) a virus-like particle carrier with at least one first attachment site, and
 - (b) at least one nicotine hapten with at least one second attachment site; wherein said second attachment site is capable of association through at least one covalent bond to said first attachment site so as to form an ordered and repetitive nicotine hapten-carrier conjugate.
88. The method of claim 87, where said composition is administered to said animal intranasally, orally, subcutaneously, transdermally, intramuscularly or intravenously.

89. The method of claim 81, wherein the animal is a human.
90. A conjugate of claim 1 for use as a medicament.
91. Use of a conjugate of claim 1 for the manufacture of a medicament for treatment of drug addiction and related diseases.
92. A pharmaceutical composition for treating nicotine addiction, palliating nicotine withdrawal symptoms, facilitating smoking cessation or preventing relapse comprising a therapeutically effective combination of the vaccine composition of claim 66 and an additional agent.
93. The composition of claim 92 wherein said additional agent is selected from the group consisting of:
 - (a) anti-depressant;
 - (b) nicotine receptor modulator;
 - (c) cannabinoid receptor antagonist;
 - (d) opioid receptor antagonist;
 - (e) monoamine oxidase inhibitor; and
 - (f) anxiolytic.
94. The composition of claim 92 wherein said additional agent is an anti-depressant selected from the group consisting of bupropion, doxepin, desipramine, clomipramine, imipramine, nortriptyline, amitriptyline, protriptyline, trimipramine, fluoxetine, fluvoxamine, paroxetine, sertraline, phenelzine, tranylcypromine, amoxapine, maprotiline, trazodone, venlafaxine, mirtazapine, their pharmaceutically active salts and their optical isomers.
95. The composition of claim 94 wherein said anti-depressant is either bupropion or a pharmaceutically acceptable salt thereof, or nortriptyline or a pharmaceutically acceptable salt thereof.

96. The composition of claim 92 wherein said additional agent is a nicotine receptor modulator selected from the group consisting of mecamylamine, SSR591813, amantadine, pempidine, dihydro-beta-erythroidine, hexamethonium, erysodine, chlorisondamine, trimethaphan camsylate, tubocurarine chloride, d-tubocurarine, varenicline, their pharmaceutically acceptable salts and their optical isomers.
97. The composition of claim 96 wherein said nicotine receptor modulator is mecamylamine or a pharmaceutically acceptable salt thereof.
98. The composition of claim 96 wherein said nicotine receptor modulator is varenicline tartrate.
99. The composition of claim 92 wherein said additional agent is a cannabinoid receptor antagonist, said cannabinoid antagonist being rimonabant.
100. The composition of claim 92 wherein said additional agent is an anxiolytic selected from the group consisting of hydroxyzine, meprobamate, buspirone, their pharmaceutical salts and their optical isomers.
101. The composition of claim 92 wherein said additional agent is clonidine.
102. The composition of claim 92 wherein said additional agent is sibutramine.
103. A method of treating tobacco addiction or nicotine addiction, palliating nicotine withdrawal symptoms, preventing relapse or facilitating smoking cessation comprising the step of administering to a patient the vaccine composition of claim 66 and an additional agent.

104. The method of claim 103 wherein said vaccine composition is administered intranasally, orally, subcutaneously, transdermally, intramuscularly or intravenously, and wherein said additional agent is administered orally or via a transdermal patch.

105. The method of claim 104 wherein said vaccine composition comprises O-succinyl-3'-hydroxymethyl-nicotine conjugated to Q β virus like particle.

106. The method of claim 103 wherein said additional agent is selected from the group consisting of:

- (a) anti-depressant;
- (b) nicotine receptor modulator;
- (c) cannabinoid receptor antagonist;
- (d) opioid receptor antagonist;
- (e) monoamine oxidase inhibitor; and
- (f) anxiolytic.

107. The method of claim 103 wherein said additional agent is an anti-depressant selected from the group consisting of bupropion, doxepin, desipramine, clomipramine, imipramine, nortriptyline, amitriptyline, protriptyline, trimipramine, fluoxetine, fluvoxamine, paroxetine, sertraline, phenelzine, tranylcypromine, amoxapine, maprotiline, trazodone, venlafaxine, mirtazapine, their pharmaceutically active salts and their optical isomers.

108. The method of claim 103 wherein said anti-depressant is either bupropion or a pharmaceutically acceptable salt thereof, or nortriptyline or a pharmaceutically acceptable salt thereof.

109. The method of claim 103 wherein said additional agent is a nicotine receptor modulator selected from the group consisting of mecamylamine, SSR591813, amantadine, pempidine, dihydro-beta-erythroidine, hexamethonium, erysodine, chlorisondamine, trimethaphan camsylate,

tubocurarine chloride, d-tubocurarine, varenicline, their pharmaceutically acceptable salts and their optical isomers.

110. The method of claim 109 wherein said nicotine receptor modulator is mecamylamine or a pharmaceutically acceptable salt thereof.

111. The method of claim 109 wherein said nicotine receptor modulator is varenicline tartrate.

112. The method of claim 103 wherein said additional agent is a cannabinoid receptor antagonist, said cannabinoid antagonist being rimonabant.

113. The method of claim 103 wherein said additional agent is an anxiolytic selected from the group consisting of hydroxyzine, meprobamate, buspirone, their pharmaceutical salts and their optical isomers.

114. The method of claim 103 wherein said additional agent is clonidine.

115. The method of claim 103 wherein said additional agent is sibutramine.